IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : Richard Hochberg
SERIAL NO. : 10/676,287
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FOR : 11β-Short Chain Substituted Estradiol Analogs and Their Use in the Treatment of Menopausal Symptoms and Estrogen Sensitive Cancer

GROUP ART UNIT : 1617
Examiner : BADIO, Barbara P.

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United States Patent and Trademark Office
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Declaration of Dr. Richard Hochberg

I, Richard Hochberg declare as follows:

1. I am the sole inventor of the subject matter of the above-referenced patent application.

2. I am a citizen of the United States of America.

3. In 1967, I received a Ph.D. in Biochemistry, from Hahnemann Medical College, in Philadelphia, PA. My thesis title was Studies on the 17β-Hydroxysteroid Dehydrogenase of Human Erythrocytes.

4. Since 1985, I have been a Professor of Obstetrics/Gynecology & Reproductive Sciences and of The Comprehensive Cancer Center, Yale University School of Medicine.

5. From 1980-1985, I held the position Associate Professor of Obstetrics and Gynecology and of Molecular Biophysics and Biochemistry, Yale University School of Medicine.

6. From 1979-80, I held the position of Assistant Professor, Department of Biochemistry, College of Physicians and Surgeons, Columbia University, Department of Medicine, Roosevelt Hospital.

7. From 1974-78, I held the position of Assistant Professor, Endocrine Biochemistry Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University.

8. In 1975, I held the position of Acting director, Gonadotrophin Radioimmunoassay Laboratory, Columbia University.

9. From 1967-74, I held the position of Research Associate, International Institute for the Study of Human Reproductive Dept. of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University. My Research Advisor was Dr. Seymour Lieberman.

10. From 1960-62, I held the position of Research Assistant, Department of Biochemistry, Fairleigh Dickinson University, School of Dentistry, Teaneck, New Jersey.

11. I am the recipient of numerous professional and technical awards and honors, including being an Editorial Board Member of *Endocrinology* (1986-1988); an Editorial Board Member of *Steroid s* (19899-1992); Corresponding Editor of Associate Editor of *J. Steroid Biochemistry and Molecular Biology* (1991-1993); an Associate Editor of *Cancer Research* (1991-2001) and the Editor-in-Chief of *Steroids* (1993-present).

12. I am the sole inventor or co-inventor of several patents/applications in the steroid area, including the present application.

13. I have published over 100 papers in peer-reviewed journals with most of the references being directed to studies on the biology, pharmacology and/or chemistry of steroids.

14. I am familiar with the above-referenced patent application and understand that Examiner Badio has maintained her rejection of claims 1-6 and 13-38 as being obvious

over the disclosure of Van den Broeck, U.S. patent no. 3,972,906 ("the 906 patent").

15. There are several reasons why the presently claimed invention would not be obvious from the '906 patent. Van den Broek and his colleagues disclosed a large number of steroid hormones that are substituted at carbon 11. Specifically relevant to the present application are a series of 11β-methoxy ethers, the major example that he discusses is the methoxy methyl ether of 17α-ethynylestradiol. (For the purpose of this discussion, I ignore the ethynyl group, which protects the 17β-hydroxyl and adds to the pharmacokinetics but does not change its action.) The disclosed compound is a very potent estrogen, and '906 patent discloses it and a large number of similar methoxy ethers as useful for treating menopausal symptoms. However, it is unlike the presently claimed compounds.

16. At the time of the '906 patent (filed in 1975), estrogen therapy was used for treating the menopausal symptoms of vaginal dryness and hot flushes. Such estrogens, were obviously, estrogenic and had stimulatory effects on the female estrogen target organs, vagina and uterus. In fact, the most commonly used method for measuring their potency was on the stimulation of uterine weight in immature or ovariectomized rodents See, Emmens, CW "Estrogens". In: Dorfman RI, ed. Methods in Hormone Research. New York: Academic Press Inc.; pages 59-111 (1962).

17. It is clear that estrogen therapy is the menopausal therapy to which the '906 patent refers. First, because this was the only type of therapy that was useful for estrogens in 1975 and second because the eventual owner of the '906 patent assignee (Organon acquired the '906 patent when it purchased the assets of Akzona, the original assignee of the '906 patent) showed that their lead 11β- methyl methoxy compounds stimulate the uterus. See, Jelinkova M, Jelinek J, de VJ, van d, V 1981 A quantitative test for oestrogenic activity using rat endometrium lactate dehydrogenase. Acta Endocrinol (Copenh) 96:389-39 ("Jelinkova"), previously submitted.

18. In Jelinkova, there is no information that they found differences in any of the 11β-methoxy ether analogs that they claim in the patent. However, had they actually

synthesized the vast list of compounds that they claim (from the teachings, they obviously did not) they would have found that the compounds of the present invention did not have the activity they desired and to which the '906 patent refers.

19. Pursuant to the present invention, a large number of 11β-ether analogs of estradiol were synthesized and tested and the results found were both surprising and are completely at odds with the '906 patent. The studies were published in the Journal of Medicinal Chemistry, copy of a paper previously submitted and attached ("the JMedChem paper"). As can be seen in Figure 2a of that publication, the methyl methoxy ether ($-CH_2O-CH_3$) is highly estrogenic as is claimed by the '906 patent, but the slightly longer ethyl ethoxy ether ($-CH_2O- CH_2CH_3$) is less estrogenic and when the 11β-sidechain is lengthened by one more methylene group to the propyl methoxy ether ($-CH_2O- CH_2CH_2CH_3$) of the present invention, it is essentially devoid of estrogenic activity, as is the longer-chained butyl methoxy ether ($-CH_2O- CH_2CH_2CH_2CH_3$). In fact, the latter 2 compounds, instead of being estrogenic, they are in fact, ***antiestrogenic***, an undesirable activity as taught by the '906 patent. These compounds inhibit the stimulatory effect of estradiol (Figure 2b) of the enclosed JMed Chem paper. This assay was performed with human uterine cells in culture, a well known assay of estrogenic potency. See, Littlefield, et al., "A simple and sensitive microtiter plate estrogen bioassay based on stimulation of alkaline phosphatase in Ishikawa cells: Estrogenic action of Δ^5 adrenal steroids." *Endocrinology*, 127:2757-2762 (1990). Had the inventors of the '906 patent synthesized the compounds that they described and tested them in their own assay, they would have found that they did not posses the estrogenic activity that they desired.

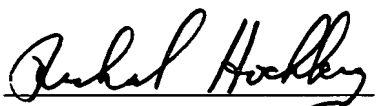
20. It is obvious from the '906 patent and the subsequent paper Jelinkova, that the activity of compounds according to the present invention was neither expected nor taught in the '906 patent.

21. Although antiestrogens, the present compounds are useful for treating menopausal symptoms because some antiestrogens (such as the unrelated tamoxifen), that are

antiestrogenic in vagina, uterus, breast, brain, are estrogenic in other tissues such as liver (reducing plasma lipids) and in stimulating bone. See, Jordan, VC, "Chemosuppression of breast cancer with tamoxifen: laboratory evidence and future clinical investigations." *Cancer Invest*, 6:589-595 (1988).

22. These compounds are now termed selective estrogen receptor modulators (SERMs) indicating that their estrogenic effects are tissue selective (for a review see the attached Jordan VC 1998 Designer Estrogens. Scientific American October:61-67). In the present invention, we showed that 11β-substituted estrogens that are antiestrogenic *in vivo* in the uterus are estrogenic in the liver (compare Figures 5a and 5b of the attached JMedChem article). Thus, they are SERMs and unlike the compounds which are described in the '906 patent. These SERMs are therapeutic in menopausal women because they reduce the risk of breast cancer (inhibiting estrogenic effects in breast) while stimulating bone and reduce circulating lipids. The '906 patent was filed at least 12 years before it was known that SERMs existed and had the inventors of the '906 patent synthesized and tested those 11β-methoxy ethers (they clearly did not even do that) that were synthesized and tested pursuant to the present invention, they would not have found the requisite estrogenic activity that the '906 invention requires. In fact, at the time of the '906 patent it would have been counterintuitive to think that antiestrogens would be useful for treatment of the symptoms of menopause.

23. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 5/2/2007 

Richard Hochberg, Ph.D.